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The role of hemoglobin A1c in the assessment of diabetes and cardiovascular risk

ABSTRACT

Hemoglobin A1c (HbA1c) is a widely used tool for diagnosing, screening, and managing patients with diabetes; however, proper application and interpretation of the HbA1c test is crucial to master for accurate assessment of patients. It also has become the standard test in population-based studies for evaluating the relationship between glycemic control and cardiovascular risk. Results from large clinical trials support the modern perspective that the HbA1c target should be personalized according to the risks and benefits of glycemic control. This likely is most important in patients with diabetes and elevated cardiovascular risk in whom achieving low HbA1c levels early in the natural history may be the most beneficial.

KEY POINTS

An HbA1c level ≥ 6.5% is the diagnostic cutoff used for diabetes diagnosis; patients with prediabetes have HbA1c values of 5.7% to 6.4%.

HbA1c is formed by the glycation of hemoglobin, thus HbA1c may be difficult to interpret in patients with medical disorders affecting red blood cell survival or glycosylation.

The use of HbA1c monitoring to manage patients with diabetes should include target levels that are tailored according to the risks and benefits of glycemic control, especially cardiovascular risks.

Although commonly used by population studies as a risk indicator for diabetes and cardiovascular complications, HbA1c may misrepresent the glycemic "big picture."

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Since its widespread introduction into routine clinical practice nearly 2 decades ago, hemoglobin A1c (HbA1c) measurement has become an integral tool for the diagnosis and management of diabetes mellitus. It is frequently used in both the care of individuals and in landmark population-based clinical trials. It also serves as a surrogate marker of glycemic control and is a key risk indicator for diabetes-associated microvascular and macrovascular complications and mortality.

With so much importance placed on one laboratory value, it is imperative to remember that the test is imperfect, with pitfalls both in accuracy and interpretation. The purpose of this review is to provide a broad understanding of HbA1c and how it can be optimally applied to patient management and the assessment of diabetes and cardiovascular (CV) risk.

HbA1c TESTING, BACKGROUND

HbA1c was first discovered in 1955, but elevated HbA1c levels in diabetes patients were not noted until 1968.[1] Another 8 years passed before HbA1c was correlated with blood glucose values in hospitalized patients with diabetes and was proposed for monitoring glycemia.[2]

Biochemically, HbA1c forms through a nonenzymatic reaction in which glucose attaches to the valine amino terminal of one or both beta chains of hemoglobin A. This compound can be separated out from nonglycated hemoglobin and from other glycated hemoglobin molecules through various methods, such as high performance liquid chromatography or immunoassay.[3]

During the first few years of clinical use, HbA1c measures were inconsistent. The publication of the Diabetes Control and Complications Trial (DCCT) in 1993[3] made the importance of precise HbA1c measurement apparent. This study found that the approximate 2% difference in HbA1c between standard- and intensive-insulin therapy groups resulted in dramatically reduced risk of microvascular disease

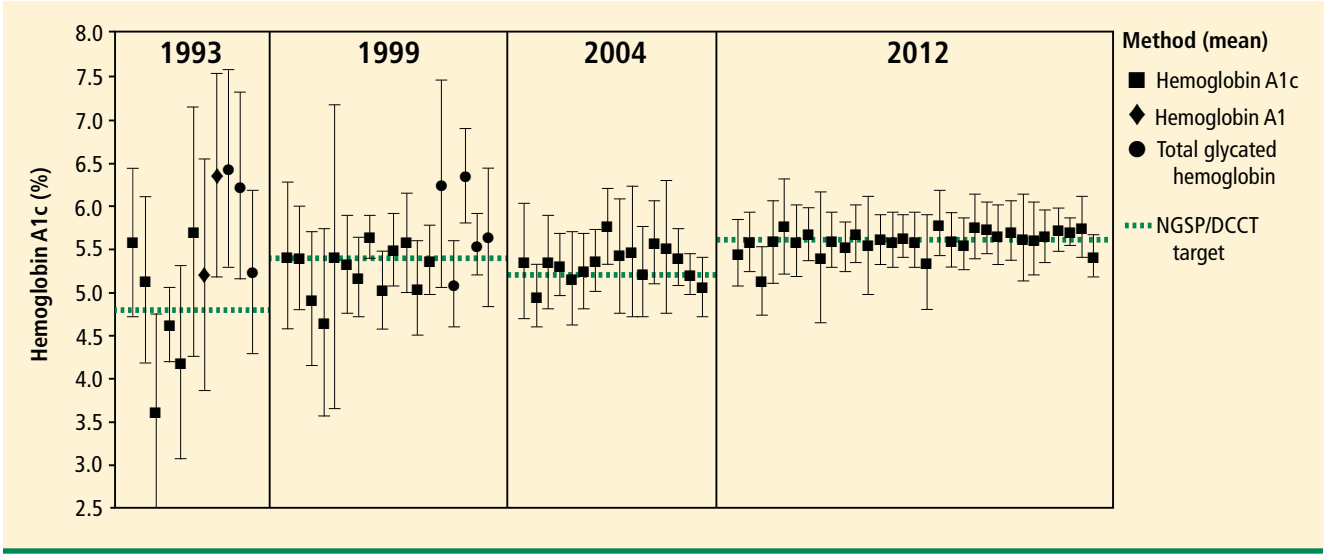

FIGURE 1. Enhanced reproducibility of hemoglobin A1c over time.[7] Shown as mean (± 2 standard deviations) of methods compared with NGSP/DCCT target in 1993, 1999, 2004, and 2012. DCCT = Diabetes Control and Complications Trial; NGSP = National Glycohemoglobin Standardization Program

in patients with type 1 diabetes. The continuation of the DCCT, the Epidemiology of Diabetes Interventions and Complications trial,[4] and a study of patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS),[5] further supported the relationship between sustaining a lower average HbA1c over time and improved patient outcomes, including CV events and mortality. Given the implications of small changes in HbA1c on morbidity, the need to reduce error margins in measurement became apparent.

The NGSP (formerly the National Glycohemoglobin Standardization Program) was founded in 1996 to regulate HbA1c measurements to DCCT standards.[6] This program, now international in scope through involvement with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), calibrates HbA1c measurements by outside laboratories and manufacturers to reference standards. Laboratories and manufacturers that measure HbA1c certify through IFCC/NGSP and participate in yearly surveys to ensure inter-laboratory reproducibility. Through this successful program, standardization and accuracy of HbA1c measurements greatly improved from 1993 to 2012 (**Figure 1**).[1,6,7] Largely owing to this fact, HbA1c was approved as a diagnostic tool by the American Diabetes Association (ADA) in 2009;[8] the test has become a key measure for diagnosing, screening, and monitoring diabetes.

The HbA1c level is affected by the blood glucose concentration, the duration of red blood cell (RBC) exposure to varying concentrations, and RBC quantity. HbA1c most accurately reflects the previous 2 to 3 months of glycemic control in the setting of the usual RBC life span of 120 days.[9] As a relatively long-term indicator of glycemic control, it may not accurately represent acute improvements or deteriorations in glycemia. Recent factors affecting glycemia must be considered, as HbA1c represents a weighted average glucose with 50% contribution from the preceding month.[10]

HbA1c must be interpreted with caution. In nonpregnant adults, HbA1c is often falsely low in conditions that reduce the number of glycosylated RBCs, such as hemolysis, splenomegaly, chronic kidney disease, cirrhosis, hemorrhage, blood transfusions, use of erythropoiesis-stimulating agents, and certain hemoglobinopathies (ie, HbS, HbC, HbF). Alternately, HbA1c is elevated in other hemoglobinopathies and in conditions that result in decreased RBC turnover such as iron or vitamin B12-deficiency anemia.[11–13]

The 2008 A1c-Derived Average Glucose study group (507 participants from 10 international centers) used linear regression analysis to correlate HbA1c drawn every 3 months with average blood glucose readings taken during those 3 months. Results from participants without diabetes were compared with patients with type 1 or type 2 diabetes.[14] The resulting

TABLE 1
Hemoglobin A1c (HbA1c) and corresponding estimated average glucose

HbA1c (%)	Mean plasma glucose (mg/dL)	IFCC units (mmol/mol)
6	126	42
6.5	141	48
7	154	53
7.5	169	59
8	183	64
8.5	198	69
9	212	75
9.5	226	80
10	240	86
11	269	97
12	298	108

IFCC = International Federation of Clinical Chemistry and Laboratory Medicine.

significant correlation between HbA1c and average blood glucose readings (coefficient of determination 0.84, P <.0001) became the standard for estimating glycemia from HbA1c (**Table 1**).

DIAGNOSIS, SCREENING FOR DIABETES

HbA1c was accepted by the ADA as a diagnostic test for diabetes in 2009[4] and the World Health Organization (WHO) in 2011,[13] although the WHO recommended alternate methods for diagnosis given concerns about test availability, cost, and accuracy in the developing world.[15]

Advantages to HbA1c use in diagnosis include standardization of measurement, convenience as a single blood-draw that does not require fasting, minimal day-to-day variability, and preanalytic sample stability. Although point-of-care testing for HbA1c is widely available, it is not recommended for diagnostic use because these assays are generally not IFCC/NGSP certified and do not undergo the same proficiency testing as laboratory samples.[12,16]

The 1997 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[17] encouraged that diagnosis be based on the glycemic level at which microvascular complications develop. Using fasting plasma glucose (FPG), 2-hour postprandial plasma glucose, and funduscopic data from several large epidemiologic studies, the committee established that increased risk of diabetic retinopathy occurs at

TABLE 2
Criteria for the diagnosis of diabetes

Measurement	ADA 2015 diagnostic values
Hemoglobin A1c	≥ 6.5% (48 mmol/mol)
Fasting plasma glucose	≥ 126 mg/dL (7.0 mmol/L)
2-Hour postprandial plasma glucose	≥ 200 mg/dL (11.1 mmol/L)

ADA = American Diabetes Association.

Based on information in American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In: Standards of Medical Care in Diabetes—2015. Diabetes Care 2015; 38(suppl 1):S8–S16.

FPG levels greater than or equal to 126 mg/dL (7.0 mmol/L). Subsequent studies analyzed sensitivity and specificity correlations between FPG levels above 126 mg/dL and HbA1c in an effort to define cutoffs for HbA1c as a diagnostic tool; however, their results lacked clear clinical relevance.[18–20]

In 2003, the DETECT-2 trial analyzed HbA1c levels in more than 28,000 participants to determine HbA1c diagnostic definitions based on microvascular complications.[21] Evaluating HbA1c in 0.5% increments, investigators found that the incidence of diabetic retinopathy rose above baseline at HbA1c of 6.5%, the now accepted diagnostic value. It is important to note that this cutoff makes HbA1c less sensitive than other diagnostic indicators, which if applied to the same number of individuals, would result in up to one-third more patients diagnosed with diabetes. However, the lower sensitivity is balanced by higher screening rates given HbA1c accessibility.[16]

Diabetes can be diagnosed according to the criteria in **Table 2**, using venous plasma samples for HbA1c and glucose measurements. FPG assessment, both alone and as part of a 2-hour oral glucose tolerance test (OGTT), requires a minimum 8-hour fast. Although it is more cumbersome for both patients and practitioners, the 2-hour OGTT remains the technical standard diagnostic test for diabetes. It can formally identify patients with impaired fasting glucose and impaired glucose tolerance, which are markers of impaired beta cell function and future progression to frank diabetes mellitus.

In the presence of clear symptoms of hyperglycemia such as blurry vision, polyuria, polydipsia, weight loss, and a random plasma glucose value ≥ 200 mg/dL (11.1 mmol/L), a single laboratory measurement fit-

TABLE 3
Diabetes risk criteria for screening nonpregnant adults

Age ≥ 45

BMI ≥ 25 kg/m^2 or ≥ 23 kg/m^2 in Asian populations

First-degree relative with diabetes

High-risk race/ethnicity (African American, Latino, Native American, Asian, Pacific Islander)

Women with history of gestational diabetes mellitus or who delivered a baby weighing > 9 lb (4 kg)

Hypertension (≥ 140/90 mm Hg or on therapy for hypertension)

Dyslipidemia: HDL cholesterol < 35 mg/dL (0.90 mmol/L), triglyceride > 250 mg/dL (2.82 mmol/L), or both

Women with polycystic ovary syndrome

Prior history of HbA1c ≥ 5.7%, IGT, or IFG

Acanthosis nigricans, severe obesity, or other conditions associated with insulin resistance

History of cardiovascular disease

Physical inactivity

BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

Based on information in American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In: Standards of Medical Care in Diabetes—2015. Diabetes Care 2015; 38(suppl 1):S8–S16.

TABLE 4
Criteria for identifying prediabetes

Measurement	ADA 2015 criteria[16]	WHO 2006/2011 criteria[13,15]
Hemoglobin A1c	5.7%–6.4% (39–46 mmol/mol)	6.0%–6.5% (42–48 mmol/mol)
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L)	110–125 mg/dL (6.1–6.9 mmol/L)
2-Hour postprandial plasma glucose	140–199 mg/dL (7.8–11.0 mmol/L)	140–200 mg/dL (7.8–11.1 mmol/L)

ADA = American Diabetes Association; WHO = World Health Organization.

ting any of the three diagnostic criteria confirms the diagnosis of diabetes. In the absence of these symptoms, one positive test must be repeated and remain positive in order to confirm diabetes. As an alternative to repeating the original diagnostic test, two of the three criteria may be positive at any one time to make the diagnosis.[13,16]

Routine screening for diabetes using HbA1c should be based on risk in the absence of symptoms (**Table 3**). The ADA recommends screening at 3-year intervals if an initial screen is within normal limits or yearly in individuals with prediabetes or a change in risk status.[16] Screening also is recommended for patients on medications that increase the risk of hyperglycemia (eg, glucocorticoids, thiazides, and atypical antipsychotics).

Individuals with prediabetes are identified as having impaired fasting glucose and impaired glucose tolerance based on 2-hour OGTT, FPG, or HbA1c (**Table 4**). Those with HbA1c values 6.00% to 6.49% are considered by the ADA and WHO to have the highest risk of developing diabetes.[13,15,16] This range is based primarily on a 2010 systematic review[22] evaluating the relationship between HbA1c and progression to diabetes in studies involving more than 44,000 participants. Patients with HbA1c of 6.0% or above had a 5-year risk of progression to diabetes between 25% and 50%, 20 times higher than those with HbA1c less than 5%.[22] The ADA-defined lower limit for diagnosing prediabetes (HbA1c ≥ 5.7%) is based on a 2011 analysis of National Health and Nutrition Examination Survey data.[23] In that study, adults with HbA1c levels at or above 5.7% were at similar risk of developing frank type 2 diabetes and CV disease (41.3% over 7.5 years and 13.3% over 10 years, respectively) as the 3,234 participants in the Diabetes Prevention Program, a prospective, population-based study evaluating the risk of incident diabetes.[23,24]

MONITORING PATIENTS WITH DIABETES

HbA1c should be performed every 3 months in patients with known diabetes and can be spaced to twice yearly in patients meeting treatment goals on stable therapy.

While not recommended for diagnosis, point-of-care testing of HbA1c has been endorsed by the ADA for monitoring patients with diabetes. Studies have shown that a higher percentage of patients achieve HbA1c targets with treatment adjustment based on point-of-care testing of HbA1c at the time of visit vs usual laboratory monitoring.[16,25]

Goal HbA1c levels in patients with diabetes should be patient-tailored, as outlined in **Figure 2**. For example, stricter control with HbA1c (≤ 6.5%) may be desired in a young, otherwise healthy individual, whereas an HbA1c of 8% may be appropriate in a patient with multiple comorbidities.[26]

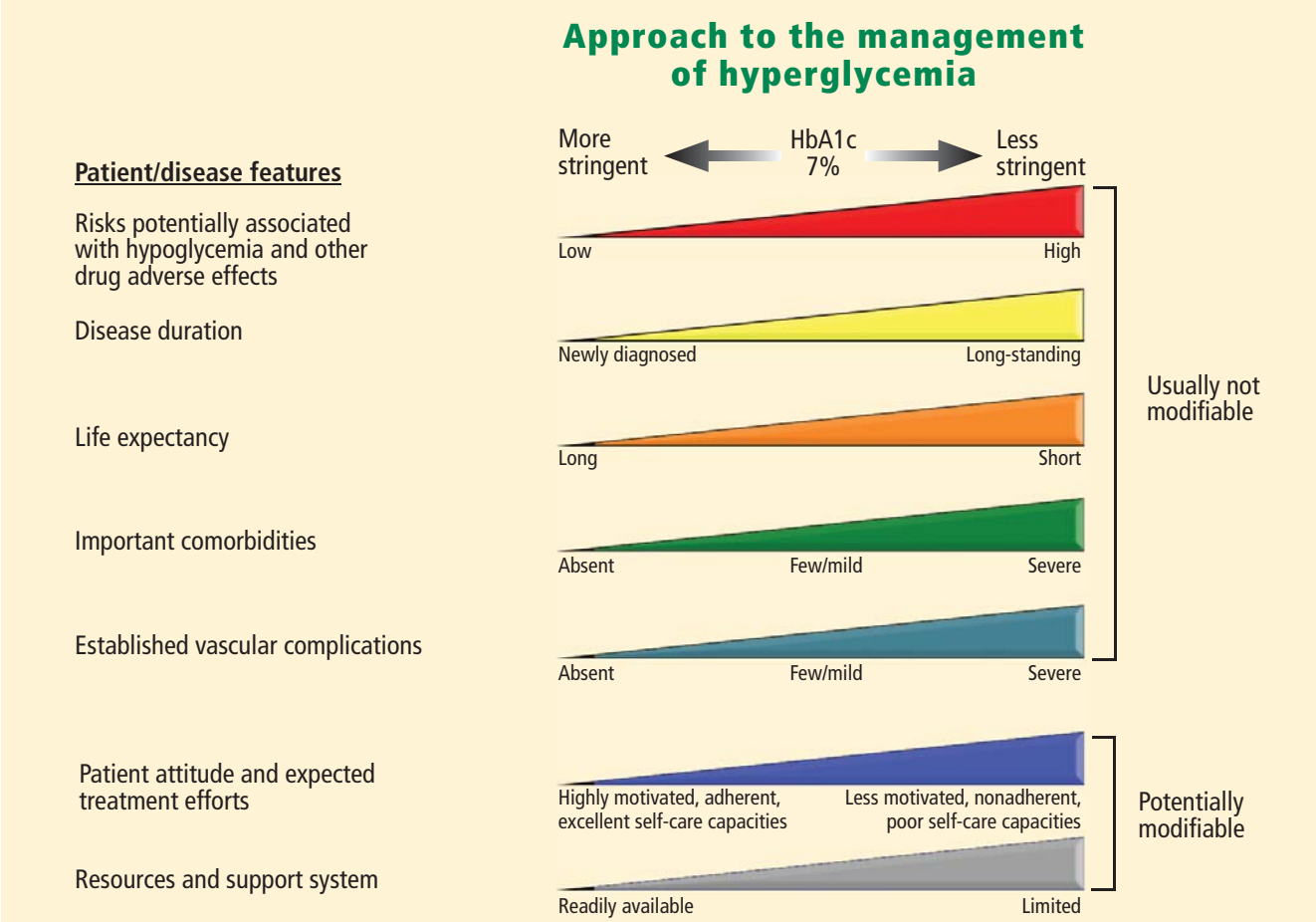

FIGURE 2. Schematic for setting hemoglobin A1c (HbA1c) goals according to a patient-tailored approach.

Reprinted with permission from: Inzucchi SI, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: 2015: A patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140–149.

HbA1c AND CARDIOVASCULAR RISK

HbA1c has been established as a strong predictor of CV events and mortality in patients with diabetes despite the absence of firm evidence that glycemic control modifies this risk substantially over time.[27] Results from the UKPDS and DCCT trials lend strong support to the hypothesis that glycemic control early in the course of disease provides preventive benefit.[3–5] In contrast, three major trials that enrolled older patients at higher baseline risk showed no mortality or CV benefit of tighter glycemic control.[28–30] One of these, the Action to Control Cardiovascular Risk in Diabetes trial,[28] found increased mortality risk in the intensive glycemic-control arm among those who did not achieve the HbA1c target, illustrating the complexity of interpreting HbA1c in clinical practice.

While HbA1c may predict the risk of mortality and CV events in diabetes populations, it is unlikely to be a strong predictor in patients without established diabetes. Analysis of data from the Emerging Risk Factors Collaboration indicates that below the HbA1c diagnostic threshold of diabetes (< 6.5%), HbA1c is less predictive than stronger risk factors such as lipids.[31] In this retrospective analysis, which included a cohort of more than 200,000 individuals without diabetes, the risk model to predict CV events was not enhanced significantly by the addition of HbA1c information.

MISREPRESENTING THE GLYCEMIC 'BIG PICTURE'

Aside from the previously discussed medical conditions that may affect HbA1c accuracy, other factors may complicate HbA1c interpretation. Recent studies raised concern about the generalizability of

HbA1c across racial and ethnic groups. A 2010 study of non-Hispanic black and white participants without diabetes revealed that black participants had higher HbA1c levels across the glycemic continuum.[32] In the past, concern was raised that these HbA1c elevations were related simply to poorer glycemic management and healthcare disparities. However, a study using data from the Diabetes Prevention Program compared HbA1c in five racial and ethnic groups and found that racial and ethnic minorities had higher HbA1c levels after adjusting for demographics, socioeconomics, and anthropometrics.[33] This suggests that racial-genetic differences in RBC survival or glycation of hemoglobin may affect HbA1c. These studies did not assess for the presence of hemoglobinopathies despite higher prevalence in certain ethnic groups.

One critique of the HbA1c assay is that HbA1c does not reflect glycemic variability. A 2007 study analyzing DCCT data found that participants with similar HbA1c levels had dissimilar mean plasma glucose (MPG) levels and glucose variability (standard deviation of MPG).[34] The authors provided an example of two patients with identical HbA1c and MPG but disparate glucose variability. The patient with higher glucose variability had a 35% to 45% excess risk of hypoglycemia. Failure of HbA1c to clearly define those at risk for frequent hypoglycemic events is problematic, since hypoglycemia is an identified risk factor for CV disease and morbidity.[35,36] Of perhaps greatest concern is that an elevated HbA1c may be a common presentation of variability in the elderly. One study showed that more than 60% of elderly patients taking insulin with an average HbA1c above 8% had several hypoglycemic events per week, and based on elevated HbA1c, they may be advised to increase insulin dosing.[37]

Glucose variability itself, including wide postprandial excursions, may be a risk factor for CV disease. The recent FLAT-SUGAR trial used HbA1c and continuous glucose monitoring to assess glycemic control and CV risk markers in participants on basal-bolus insulin therapy plus metformin versus subjects on basal insulin, metformin, and a GLP-1 agonist intended to reduce postprandial glucose excursions.[38] Although groups achieved similar target HbA1c levels, the intervention group had fewer glycemic excursions as well as reductions in some CV risk markers.

Alternatives to HbA1c are available for monitoring glycemic control. The monosaccharide 1,5-anhydroglucitol, a short-term marker of glycemia, competes with glucose for reabsorption in the kidney. In patients with normal renal function, low serum levels represent short-term hyperglycemia. Fructosamine and glycated albumin, formed by the glycation of proteins, reflect glycemia over the 2- to 4-week protein half-life.[39] Fructosamine measurement is confounded by the presence of low molecular weight substances such as bilirubin and uric acid; therefore, it may not be useful in medically complex patients. Glycated albumin is not affected by these substances; it may also be useful in patients in whom variations in RBC survival make HbA1c unreliable.[11,40] Despite the growing body of research about their usefulness, these tests lack the stringent standardization of HbA1c and have not been vetted for use in large clinical trials. Thus, their use in routine clinical practice remains controversial.

CONCLUSION

The focus on HbA1c during the last 40 years has resulted in enhanced test accuracy, availability, and use among patients and providers in the care of diabetes. Because HbA1c has become the standard in how population-based studies evaluate the effects of glycemic control on disease progression and complications, it serves as the basis for guidelines that address diabetes and CV risk definition and management. Although HbA1c may seem familiar, there is much not known about test interpretation and how it may actually miss the mark. As HbA1c use continues, these concerns need to be clarified to optimize the screening, diagnosis, and care of patients with diabetes and CV disease.

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